Insightful Moments™

PTC EDUCATIONAL SERIES

Understanding the FDA approval process for gene therapies

Table of Contents

About PTC Therapeutics

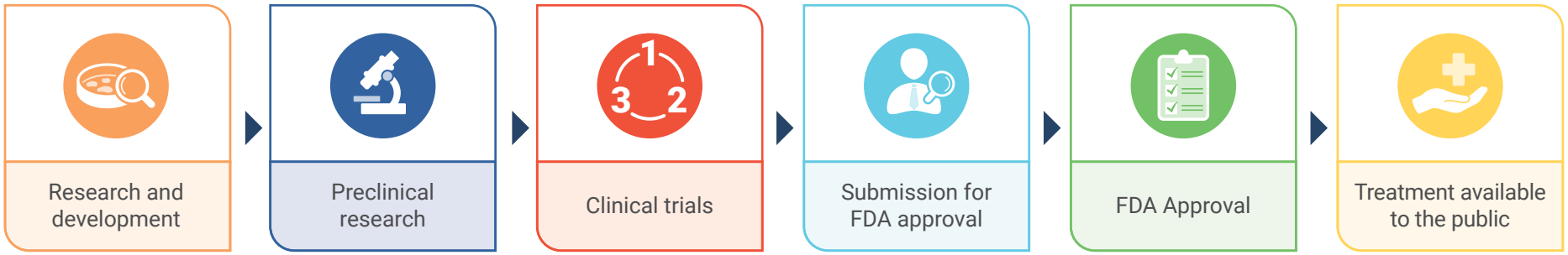
PTC Therapeutics is a science-driven, global biopharmaceutical company focused on the discovery, development, and commercialization of clinically differentiated medicines that provide benefits to patients with rare disorders.

Our mission is to provide access to best-in-class treatments for patients with an unmet medical need, using our ability to globally commercialize products as the foundation to drive investment in a robust and diversified pipeline of transformative medicines.

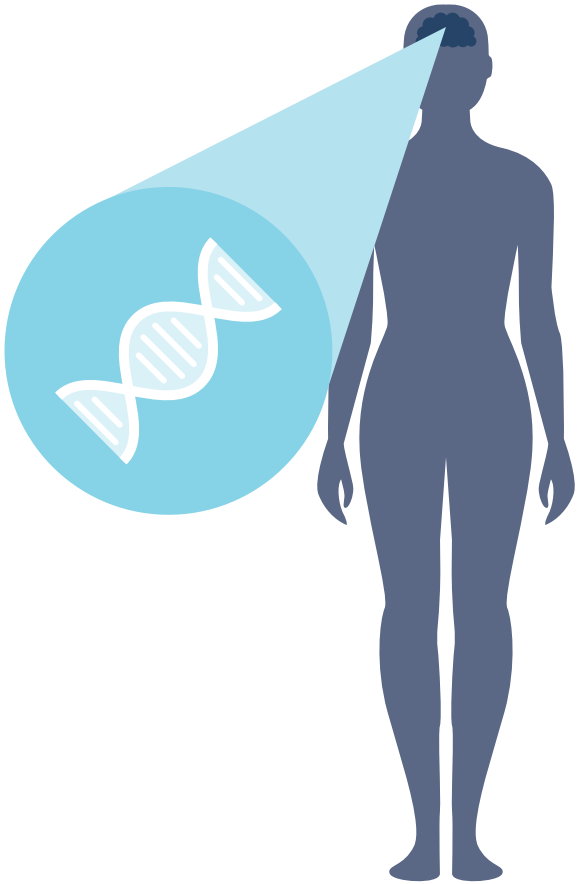
We continually invest in cutting-edge research programs in hopes of finding treatment options for patients suffering from rare diseases. PTC is committed to bringing innovative new therapies, like gene therapy, to the patients and communities that need them.

An overview of the development and FDA approval process for new treatments

New treatments are studied, tested, and reviewed thoroughly before they're approved and available to the public. To ensure new treatment options are safe and effective, drug developers and the US Food and Drug Administration (FDA) follow the process below.



Researching and developing a new drug



The first step to making any drug available to the public is the initial research and development. A pharmaceutical company will often begin researching options for a new treatment when there is an unmet clinical need. **An unmet clinical need could be a condition for which treatment or diagnosis is not sufficiently addressed by available therapies.**

The process of developing a new drug starts with identifying a biological target. A target is a molecule in the body—such as a protein, gene, or RNA—that, upon contact with the drug, results in a beneficial effect for the patient. Although a potential target may show ideal results in a laboratory setting, researchers need to be sure the target (and therefore the drug) will be safe and effective in people.

Researching and developing a new drug can be **costly and time consuming**. The full research, development, and approval process can last 12 to 15 years. **For every 5,000 to 10,000 drug formulations, only 1 will receive FDA approval.**

Preclinical research

Pharmaceutical companies must prove a drug is effective and won't cause harm before it can be tested in people during a clinical trial. There are 2 ways in which companies test drugs:

1 IN VITRO

Meaning "in glass," for example, in a test tube or a petri dish

2 IN VIVO

Meaning "in the living organism," for example, animal testing

INVESTIGATIVE NEW DRUG APPLICATION

Before clinical trials can begin, the manufacturer must submit an Investigational New Drug (IND) application, which provides the US Food and Drug Administration (FDA) with data from preclinical research, as well as information about how the drug is made and how they plan to study it.

DESIGNING THE PROTOCOL

The drug developer designs a study plan, called a protocol, which is submitted to the FDA as part of the IND.

The protocol includes detailed information about:

PARTICIPANTS

How many and who qualifies

DURATION

How long each phase and the overall study will last

METHOD OF COMPARISON

Whether there will be a control group to compare the data against

ASSESSMENT

What will be measured and how will it be assessed

ANALYSIS OF DATA

How the data will be analyzed or interpreted

Phases of a clinical trial

Once the study protocol is approved by the FDA, drug developers can begin the clinical trial. Each clinical trial program is structured differently, but drugs are typically evaluated in 3 phases.

PHASE 1

IS IT SAFE?

Purpose: Safety and dosage

PHASE 2

IS IT EFFECTIVE?

Purpose: Efficacy and side effects

PHASE 3

CONFIRM EFFECTIVENESS AND SAFETY

Purpose: Efficacy and monitoring long-term side effects

Clinical trials typically span several years, although some are conducted over the course of months. The number of participants will also vary depending on the size of the population with the disease and eligibility criteria.

Find information about specific US clinical trials at clinicaltrials.gov.

Before participating in a clinical trial, volunteers sign an informed consent document. This is intended to protect participants by ensuring they understand the potential risks, benefits, and alternatives to the study. Participants can withdraw from a study at any point, even if the study is not over.

Rare disease drug approvals

Any drug in development follows the same rigorous process to evaluate safety and effectiveness, including treatments for rare diseases.

The FDA recognizes rare diseases as conditions that affect fewer than 200,000 people in the United States. Many of these conditions do not have any approved treatments. Some conditions may be life threatening, so the FDA has special rules to help expedite the approval process for rare disease treatments and make them available to the people who need them. **This process is called priority review.**

Priority Review

A designation granted to drugs that treat serious conditions and that, if approved, would significantly improve the safety or effectiveness of the treatment as compared to standard treatment.

Here are a few notes regarding the FDA's process in approving treatments for rare diseases:

Priority review can be given to drugs that are the first and only treatment for a specific disease

Priority review can be given to drugs that provide a significant improvement over the currently available treatments for a specific disease

Rare disease populations are small, so the FDA will allow smaller samples to be studied for approval

Treatments for **rare diseases are studied with the same rigor as any drug in development** but may follow a slightly different process because of the small population sizes.

Submitting a new drug for FDA approval

When a clinical trial shows promising results, the pharmaceutical company submits a New Drug Application (NDA) to the FDA. There are similar processes for approving treatments known as biologics, which are made from or contain components of living organisms. **Gene therapies are a type of biologic, and when a company seeks FDA review, they submit a Biologics License Application (BLA).** These applications contain detailed information on effectiveness and safety results from clinical trials, animal testing, the drug's or biologic's ingredients, how it behaves in the body, and how it will be manufactured, processed, and packaged.

Before the product can be sold and prescribed to patients, the FDA must evaluate it and determine that the health benefits outweigh its known risks. The review process takes place through 1 of the FDA's 2 regulatory centers, the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER). Both the CBER and CDER adhere to the following framework when determining whether to approve a product:

Analysis of available treatments—FDA reviewers evaluate current treatment options for the condition or illness, which provides context when considering the risks and benefits of a new drug or biologic.

Assessment of benefits and risks from clinical data—Findings from clinical trials determine if a new product gets approved. Developers are generally expected to submit results from 2 clinical trials, with convincing evidence that the product will benefit the target population.

Strategies for managing risks—All drugs and biologics submitted for approval must include risk management strategies, including an FDA-approved drug label, which clearly describes its benefits and risks, and how the risks can be detected and managed.

Approving a new treatment

When a drug developer files a New Drug Application (NDA) or a Biologics License Application (BLA), the FDA's review team has 6 to 10 months to decide whether to approve the drug or biologic. On occasion, the FDA will request additional advice and recommendations from an advisory committee comprised of scientific experts, such as researchers and physicians, as well as members of the public, including patient representatives. Advisory committees are designed to provide a diverse, non-governmental perspective during the FDA approval process.

Once the drug or biologic receives approval, it becomes available to the public.

ACCESSING APPROVED MEDICATIONS AND TREATMENTS

A significant investment is made to achieve and maintain the level of quality and safety required for FDA approval. As a result, medications and treatments can be costly. To assist patients and families, there are several options to help access approved treatments.

- Private health insurance
- Medicare/Medicaid
- Patient-assistance programs
- Support from nonprofit organizations

What is gene therapy?

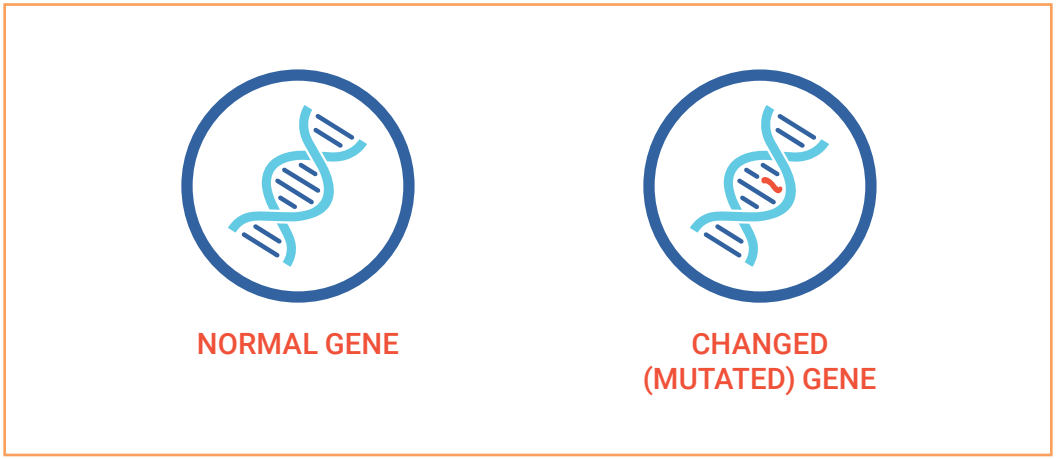
GENE THERAPIES TREAT DISORDERS CAUSED BY MUTATIONS, OR ALTERATIONS, WITHIN A SINGLE GENE

Genes are found within cells and are made up of DNA. They carry information that determines the traits and characteristics passed down to individuals from their parents. Each person gets 2 copies of every gene, 1 from each parent. These genes influence how a person looks, including skin, hair, and eye color.

Genes also provide instructions to make building blocks called proteins. These proteins support important functions in the body like digestion, communication between different parts of the body, energy production, and growth.

Sometimes there can be an alteration within a copy of a gene, called a genetic mutation. This change can be harmful and lead to genetic health problems or disorders.

Gene therapies are treatments made especially for genetic conditions. They provide a working copy of the altered gene.

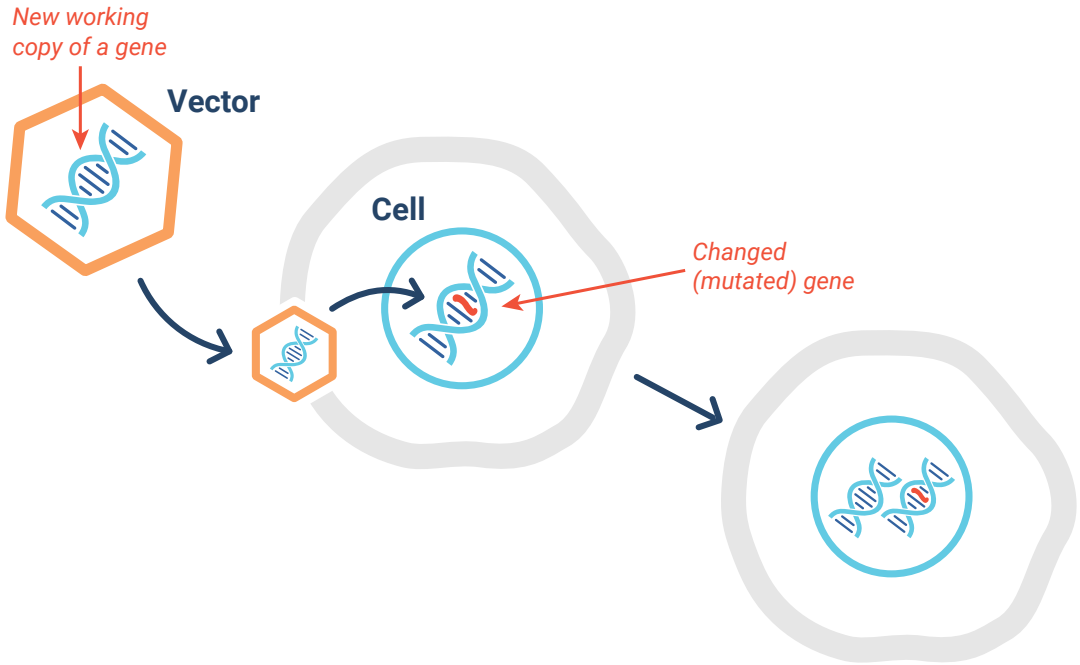


How gene therapy works

INTRODUCING WORKING GENES INTO THE BODY

The currently available gene therapies work by adding genes to the body (while the non-working gene remains) to help fight or treat specific health problems or disorders. Research continues to investigate different types of gene therapies and other ways in which they can work to help address health problems.

Gene therapy can be used to modify cells inside the body. The carrier or vector delivering the gene is injected into a vein or into the part of the body that is most affected by the non-working gene. Because gene therapies contain components of living organisms—the working copy of the gene—they are considered biologics.



WHAT IS A VECTOR?

A vector is a delivery vehicle, typically a modified virus, that carries the new live, working gene into the body and targets specific cells. Vectors are safe to use in gene therapy because the virus has been modified so that it can't make the recipient sick.

Ensuring medications are high quality

CURRENT GOOD MANUFACTURING PRACTICE

Pharmaceutical companies strive to make their products as safe and effective as possible so they can provide the most benefit to people who need them. The FDA regulates all pharmaceuticals and biologics by enforcing Current Good Manufacturing Practices (CGMPs).

CGMPs are in place to protect the public. Everything about a drug or biologic is regulated, from the temperature used to store it to how it's packaged. Here are some manufacturing requirements enforced by the FDA:

System for detecting product deviations

Label requirements

Proper ingredient storage

Routine equipment cleaning

The FDA reviews the manufacturer's compliance with CGMPs and inspects the facility during the drug approval process. **Facilities are inspected by highly trained FDA staff** using a uniform approach. The FDA works with pharmaceutical companies, such as PTC, **to ensure the right facilities and systems are in place to properly and safely manufacture the treatment**.

The FDA approval process for gene therapies

Drug developers and researchers rigorously study and test new drugs for safety and efficacy

The FDA follows strict guidelines when considering new treatments for approval

Gene therapies are studied and evaluated with the same rigor as any other FDA-approved drug

The FDA regulates all pharmaceuticals by enforcing Current Good Manufacturing Practices (CGMPs)

PTC is committed to the rare disease community. If you'd like additional information or have any questions about the topics in this brochure, please reach out to patientengagement@ptcbio.com.